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Reprofiling the Antidiabetic Drugs to Restrict SARS-CoV-2: An In-Silico Approach

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ABSTRACT

The current COVID-19 pandemic scenario was sparked by three zoonotic coronaviruses that have been linked to large-scale disease outbreaks such as Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Swine Acute Diarrhea Syndrome (SADS) in the previous two decades. The causative virus was initially referred to as "novel coronavirus 2019" (2019-nCoV) by the World Health Organization (WHO), but it was later termed as “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2) by the international committee of the Coronavirus Study Group (CSG), and the infection was renamed as "coronavirus disease 2019" (COVID-19) by WHO. The binding receptor for SARS-CoV-2 is Angiotensin-converting enzyme 2 (ACE2) of host body. Diabetes mellitus is highly associated with increased ACE2 expression in host body. Thus, people with diabetes mellitus are more prone to COVID-19 infection and there are chances of co-morbidity and increased mortality from COVID-19 infection. Here different classes of anti-diabetic drugs were considered for the computational analysis on three different receptors of SARS-CoV-2 for the re-profiling of the drugs against the virus. Glimepiride, glipizide, gliquidone and glisentide drugs were found to be more active with respect to the standard anti-viral drugs like ritonavir, indinavir, boceprevir and atazanavir against the three main receptors of SARS-CoV-2 in terms of molecular docking. The detailed ADMET studies were carried out and it was found that the anti-diabetic drugs of sulfonyl urea group are active against the SARS-CoV-2 in terms of computational analysis.

Keywords: SARS-CoV-2, Diabetes Mellitus, Protease Enzyme, Main Protease, Papain-like Protease, RNA Dependent RNA Polymerase

1. INTRODUCTION

The present scenario of COVID-19 pandemic was started from three zoonotic coronaviruses that have been reported as the source of Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), and Swine Acute Diarrhea Syndrome (SADS) in large-scale disease outbreaks over the last two decades [1]. In 2003 and 2012, SARS and MERS triggered worldwide pandemics that took thousands of human lives, respectively, while SADS hit the swine industry in 2017. Despite the emergence of new coronavirus infections most likely

arising from China's bats by early March 2019, no international preventive action was taken. Finally, in early 2020, after multiple cases of pneumonia with an unknown etiology were reported at the end of 2019, China's National Health Commission published more information about the epidemic [2]. Initially, the causative virus was termed "novel coronavirus 2019" (2019-nCoV) by the World Health Organization (WHO), but then it was termed as "severe acute respiratory syndrome coronavirus 2" (SARS-CoV-2) by the international committee of the Coronavirus Study Group (CSG), and the infection was termed as "coronavirus disease 2019" (COVID-19) by WHO [3]. The transmission of the virus from one human to another by coughing, sneezing, and the propagation of respiratory droplets or aerosols was accepted. Moreover, disease spread was recorded in almost every country on every continent due to aerosol penetration into the upper respiratory tract and lungs during inhalation [4,5]. A mathematical model was used to see whether SARS-CoV-2 infection could be regulated by isolating and monitoring infected patients' interactions with others. Since it takes excessive time between the onset of symptoms and isolating individuals, this model suggested that isolating people and updating their interactions would be insufficient to contain the COVID-19 pandemic [6]. The transmission of the SARS-CoV-2 virus is extremely high for which no appropriate cure has yet been approved by any authority. So, preventive strategies, responsive diagnostic techniques, and the use of currently available medications need to be maintained while novel treatments are being developed [7–9].

Diabetes or diabetes mellitus is a metabolic disorder, characterized by elevated blood glucose level for a prolonged time (WHO). Which mainly occurs due to the lack of insulin hormone in the body. This happens either for decreased production of insulin by β-cells of islets of Langerhans in pancreas or for lack of interaction between body cells and insulin [10]. If left untreated, many acute complications like Diabetic Ketoacidosis (DKA), Hyperglycemic Hyperosmolar State (HHS), Lactic Acidosis (LA) [11], Nonketotic Coma [12] and many long term complications like heart disease, kidney failure, foot ulcers, stroke, and damage to the eyes [13] may occur. Diabetes can be generally classified in Type 1 diabetes, Type 2 diabetes, gestational diabetes, and some other types due to monogenic diabetes syndrome, disorder of exocrine pancreas (pancreatitis, cystic fibrosis), drugs or chemical induced (eg. glucocorticoids) [American Diabetes Association]. Type 1 Diabetes Mellitus (T1DM) or juvenile-onset diabetes or insulin-dependent diabetes mellitus (IDDM) is further classified into 2 types, Immune-Mediated and Idiopathic. T1DM is caused due to T cell mediated [14] autoimmune destruction of beta cells of pancreatic islets of langerhans, in which little or no insulin is secreted by islets of Langerhans, leading to insulin deficiency [15]. 5% to 10% of all diabetes are type 1 diabetes mellitus. Males are more susceptible for T1DM than females [16]. Type 1 diabetes is partially inherited, influenced by Human Leukocyte Antigen (HLA) class II genes namely, HLA DRB1*0301-DQA1*0501-DQ*B10201 (DR3) and HLA DRB1*0401-DQA1*0301-DQB1*0301 (DR4-DQ8) [17]. Type 2 Diabetes Mellitus (T2DM) or Non-Insulin-Dependent Diabetes Mellitus (NIDDM) is the most common form of Diabetes Mellitus. T2DM is caused due to defects in insulin secretion and insulin resistance which leads to increase in liver's glucose production [18]. Over 90% of all diabetes are type 2 diabetes mellitus [19]. T2DM is associated with various lifestyle factors like obesity, unhealthy diets, lack of physical activity, stress and urbanization [20]. T2DM generally develops in adulthood. Several Adverse childhood experiences like child abuse, neglect, household difficulties contributes to the onset of type 2 diabetes mellitus in later life [21]. Gestational diabetes is the condition in which blood glucose level is elevated during pregnancy and after delivery it disappears or improves. Prevalence of Gestational diabetes varies from 2% to 30% across the world [22]. Gestational diabetes is caused due to increase in the level of insulin antagonist hormone during the second and third trimester of pregnancy. After pregnancy few patients can suffer from another form of diabetes, mainly type 2. Gestational diabetes can be icotreated by dietary changes, blood glucose monitoring, and increased physical activity [22].

People with diabetes mellitus are more prone to COVID-19 infection and there are chances of co-morbidity and increased mortality from COVID-19 infection [23,24]. Similarly, people with diabetes mellitus are more likely to be affected by SARS CoV-2. Main mechanisms for which patients with diabetes mellitus are more susceptible to COVID-19 are - i) higher affinity cellular binding and efficient virus entry, ii) presence of any cardiovascular disease, iii) decreased function of T cell, iv) reduced viral clearance, and v) increased susceptibility to hyperinflammation and cytokine storm syndrome [25]. The binding receptor for SARS-CoV-2 is Angiotensin-converting enzyme 2 (ACE2) present in the host body [26]. ACE2 is mainly expressed in lungs and kidneys but they are also expressed in gut and brain [27]. Extensive ACE2 expression in myocardium, kidney, pancreas and alveolar AT2 cells can be the reason behind increased cellular binding with spike protein of novel coronavirus [28]. According to Rao S *et al*. Diabetes mellitus is highly associated with increased ACE2 expression inside the host body [29]. Elevated levels of furin, a protease enzyme present in the human body, is observed in patients with diabetes mellitus. This furin facilitates the entry of virus by cleaving S1 and S2 domain of the spike protein [30].

RNA dependent RNA polymerase (RdRp), Main Protease (Mpro) and Papain-like protease (PLpro) are found to be most important for restricting the central dogma of SARS-COV-2. RdRp, also called nonstructural protein 12 (Nsp 12), is one of the important enzymes for transcription and replication in retrovirus [31]. Mohammed Ahmad *et al*, identified the GTP binding domain

of this RdRp of 2019-nCoV and predicted that as a possible ligand binding site for various small molecule inhibitors. They have used computational approaches like homology modeling of nCoV RdRp, Docking studies including MD simulations and ADMET studies [32]. Coronavirus main protease (Mpro), also named as 3-chymotrypsin like protease (3CLpro) or Nsp5, can develop various functional proteins by processing or proteolytic cleavage of two polyproteins, PP1a and PP1ab. This protease cleaves at 11 conserved inter domain sites in the P1 position of PP1a and PP1ab to release various functional proteins namely RdRp, helicase, exo and endo-ribonucleases, 2′-O-ribose methyltransferase etc, and thus helps in viral replication and transcription [33,34]. Papain-like protease (PLpro), also called Nsp3, acts as deubiquitinase which deubiquitinate proteins of host cells like interferon regulatory factor 3 (IRF3) and inactivate the pathway for nuclear factor kappa-light-chain-enhancer of activated B cells (NF- kappa B), leading to immune suppression in the host cells when host is attacked by virus [35]. This PLpro cleaves the replicase polyprotein in the N terminal domain to form 3 nonstructural proteins (Nsps) like Nsp1, Nsp2 and Nsp3, which are responsible for viral replication [36,37]. In this current study we had considered different classes of marketed antidiabetic drugs and some drugs which are in clinical trials for treatment of diabetes and subjected towards the *in-silico* protease inhibition. Further top compounds towards the molecular docking studies on the above three receptors. Based on the interaction energy in all the all three receptors, the top compounds were subjected towards drug likeness, ADMET profiling and toxicity analysis using computational tools.

2. MATERIALS AND METHODS

2.1. Biological Activity Predictions of the Compounds

All the 49 anti-diabetic drug molecules along with 4 standard drugs of SARS-CoV-2 were considered for the *in-silico* biological activity prediction. The main protease enzyme (Mpro) of the SARS-CoV-2 was reported as the main target to inhibit the virus. Thus checking the protease inhibition was considered as the primary parameter of selecting molecules. The protease inhibition activity prediction of the molecules was carried out on the Molinspiration Cheminformatics Software web server (https://www.molinspiration.com/) by putting the canonical smiles in the webserver.

2.2. Molecular Docking Studies

The molecular docking study is one of the important computational approaches to determine the "Best-Fit" between the ligand and the receptor [38]. This method is widely used for lead optimization. The drug molecules with satisfying protease inhibition activity were considered for molecular docking analysis. Molecular docking was performed using the AutoDock Vina protocol [39,40]. More negative the binding affinity between the receptor and ligand, the more optimum the binding pose.

2.2.1. Protein Preparation

Docking was performed on three receptors namely Mpro, Plpro and RdRp. The protein structures were extracted from the Research Collaboratory for Structural Bioinformatics (RCSB). Mpro, Plpro and RdRp having PDB IDs: 7BRP [41], 7CMD [42] and 7D4F [43] respectively. The resolution of the three proteins are 1.80 Å, 2.59 Å and 2.57 Å respectively. This gives the rationale for selecting this protein structure, as we are also aiming to develop novel protease inhibitors against SARS-CoV2. The protein was modeled by MGL Tools 1.5.6 (Molecular Graphics Laboratory, The Scripps Research Institute, La Jolla, USA), run in a DELL system with Windows 10, 64-bit OS, 8 GB RAM, and an Intel(R) Core(TM) i5-7200U CPU with 2.5 GHz processor. In this current study atazanavir, boceprevir, indinavir and ritonavir were considered as the standard molecule. The energy minimization of all the proteins was done on the Swiss-Pdb Viewer by using the Steepest Descent method of energy minimization [44]. The Kollman charge was added followed by the addition of the polar hydrogen atoms with the help of AutoDock Tools [39]. The grid box was generated by taking the grid dimensions of 24*24*24 Å at a grid resolution of 1 Å and the grid box resolution was set according to the position of the crucial amino acids, interacted by the co-crystal ligand. The dimensions were set as grid center: x = 20.754, y = -13.468, z = 15.941 for Mpro protein (PDB ID: 7BRP), x = -29.781, y = -14.071, z = -29.867 for PLpro protein (PDB ID: 7CMD) and x = 119.703, y = 139.531, z = 145.624 for RdRp protein (PDB ID: 7D4F).

2.2.2. Ligand Preparation

Among the 49 antidiabetic molecules which fulfil the protease inhibition activity along with 4 standard molecules of SARS-CoV-2 were considered for the studies. The ligand was first sketched in ACD CHEMSKETCH software [45]. All the structure was sketched on the ChemSketch Freeware application. The ligand PDB file was prepared with the help of the PRODRG web server (http://davapc1.bioch.dundee.ac.uk/cgi-bin/prodrg) by using the topology of the structure [46]. Finally, the PDBQT files were generated by adding the gasteiger charge and assigning atoms to the AutoDock-4 (AD4) type.

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2.2.3. Analysis of Docking Protocol

The docking was done by using the AutoDock Vina script [40]. The Local Gradient Optimization approach was used as a scoring function to find the optimal binding postures for the developed lophine molecules and various proteins. The binding energy (kcal/mol) and the number of binding interactions were used to analyze the docking. The docking results were analysed using Discovery Studio Visualizer [47]. The 2D, 3D docking interaction images and the molecular surface view of the binding site domain were analysed. Binding affinity between the receptors and ligands and Hydrogen (H) bonding interaction were observed and reported along with the interacting amino acid residues. Lower the binding affinity, the higher the docking pose.

2.2.4. Docking Validation

According to the literature review, RMSD during docking validation was reported to be around less than 3 Å in one article [48] and less than 1.3 Å in another [49]. The lesser the RMSD, the greater will be the docking accuracy, thus our docking protocol was successfully validated being well within the acceptable range, using Autodock Vina [40].

2.3. Drug-Likeness Study and Molecular Properties

In this current study, the drug-likeness parameter of the compound was evaluated based on Lipinski's Rule of Five and Veber's Rule [50,51]. The top docked compounds with the highest docking score (in terms of binding energy) were considered for the drug-likeness properties. Different parameters like molecular weight, the number of hydrogen bond donors/acceptors, polar surface area, the number of rotatable bonds, partition coefficient, etc. were determined. SwissADME web server (http://www.swissadme.ch/) was used to predict the Absorption, Distribution, Metabolism and Excretion (ADME) of the molecules [52]. The SMILE format of the molecules was uploaded to the server and the results were downloaded and analyzed. The Brain Or IntestinaL EstimateD permeation method (BOILED-Egg) was used to determine the pharmacokinetics and bioavailability of the compounds [53].

2.4. Toxicity Studies

The toxicity was checked at the mcule toxicity checker web server (https://mcule.com/apps/toxicity-checker/). This web server gives results in terms of yes or no. The details toxicity was evaluated in the ProTox-II web server (https://tox-new.charite.de/protox_II/) [54]. Here different toxicological parameters like Hepatotoxicity, Carcinogenicity, Immunotoxicity, Mutagenicity LD_{50}, etc. of the top docked compounds were predicted.

3. RESULTS

3.1. Biological Activity Predictions of the Compounds

The protease inhibitor bioactivity prediction of the compounds was carried out through the Molinspiration Cheminformatics Software web server (https://www.molinspiration.com/). All the 49 anti-diabetic drugs along with 4 standard molecules were checked for the *in-silico* protease inhibitor activity. The standard anti-viral drugs atazanavir, boceprevir, indinavir and ritonavir showed the *in-silico* protease inhibition values of 0.26, 1.41, 0.66 and 0.35 respectively of which 0.26 value of atazanavir was the lowest and was considered as the cut-off value for all the 49 anti-diabetic compounds [55–59]. A total of 21 compounds showed the *in-silico* protease inhibitor value greater than equals to 0.26 as presented in table 1.

Table 1: Protease Inhibitor Scores of the compounds

SL NO	COMPOUND	Protease Inhibitor	SL NO	COMPOUND	Protease Inhibitor
1	Acetohexamide	0.28	14	Mitiglinide	0.54
2	Carbutamide	0.32	15	Nateglinide	0.59
3	Cetilistat	0.28	16	Naveglitazar	0.29
4	Denagliptin	1.32	17	Saxagliptin	1.56
5	Empagliflozin	0.28	18	Sitagliptin	0.56
6	Evogliptin	0.85	19	Tesaglitazar	0.38
7	Glibornuride	0.45	20	Vildagliptin	1.02
8	Glimepiride	0.32	21	Voglibose	0.34
9	Glipizide	0.39	---	---	---

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10	Gliquidone	0.31	22	Atazanavir	0.26
11	Glisentide	0.27	23	Boceprevir	1.41
12	Glycyclamide	0.26	24	Indinavir	0.66
13	Metahexamide	0.32	25	Ritonavir	0.35

3.2. Molecular Docking Analysis:

The molecular docking was performed by using the AutoDock Vina module [40]. All the 21 screened anti-diabetic molecules showed comparative docking score in terms of interaction affinity with respect to the four standard molecules. The values of interaction affinities are given in table 2. Glimepiride showed the binding affinity of (-) 8.0 kcal/mol, (-) 9.2 kcal/mol, (-) 8.2 kcal/mol with the Mpro, Plpro and RdRp enzymes respectively of the SARS-CoV-2, which are comparable with respect to all the four standard molecules. Along with this Glipizide and Gliquidone also showed remarkable interaction affinity with all the receptor enzymes. Glipizide showed the binding affinity of (-) 7.6 kcal/mol, (-) 9.2 kcal/mol, (-) 8.1 kcal/mol with the Mpro, Plpro and RdRp enzymes respectively and Gliquidone showed the binding affinity of (-) 8.7 kcal/mol, (-) 8.4 kcal/mol, (-) 8.2 kcal/mol with the Mpro, Plpro and RdRp enzymes respectively of the SARS-CoV-2.

Table 2: Interaction affinity of anti-diabetic molecules with Main Protease, Papain like Protease and RNA Dependent RNA Polymerase

SL NO	COMPOUND	Interaction Affinity (kcal/mol)		
		Main Protease (PDB ID: 7BRP)	Papain like Protease (PDB ID: 7CMD)	RNA Dependent RNA Polymerase (PDB ID: 7D4F)
1	Acetohexamide	-6.9	-7.8	-6.4
2	Carbutamide	-6.3	-6.9	-6.2
3	Cetilistat	-5.6	-6.7	-4.6
4	Denagliptin	-7.2	-8.1	-6.9
5	Empagliflozin	-7.4	-7.4	-6.6
6	Evogliptin	-7.0	-7.6	-6.6
7	Glibornuride	-7.0	-8.0	-7.0
8	Glimepiride	-8.0	-9.2	-8.2
9	Glipizide	-7.6	-9.2	-8.1
10	Gliquidone	-8.7	-8.4	-8.2
11	Glisentide	-7.3	-9.2	-7.7
12	Glycyclamide	-7.1	-7.7	-6.5
13	Metahexamide	-7.1	-7.8	-6.6
14	Mitiglinide	-6.6	-7.3	-6.8
15	Nateglinide	-7.0	-7.9	-6.6
16	Naveglitazar	-6.0	-7.9	-7.3
17	Saxagliptin	-6.9	-5.3	-5.4
18	Sitagliptin	-7.8	-7.9	-7.3
19	Tesaglitazar	-6.7	-7.5	-6.4
20	Vildagliptin	-7.7	-6.6	-5.8
21	Voglibose	-5.6	-5.4	-5.8
22	Ritonavir	-6.9	-7.2	-7.1
23	Indinavir	-7.8	-8.0	-7.5
24	Boceprevir	-8.2	-7.1	-6.8
25	Atazanavir	-6.8	-7.0	-6.2

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3.2.1. Binding Interaction of Glimepiride with Main Protease of SARS-CoV-2:

Glimepiride binds very well with the main protease enzyme of the SARS-CoV-2 with interaction energy of (-) 8.0 kcal/mol whereas, the four standard molecules ritonavir, indinavir, boceprevir, and atazanavir showed the interaction energy of (-) 6.9 kcal/mol, (-) 7.8 kcal/mol, (-) 8.2 kcal/mol and (-) 6.8 kcal/mol respectively. Thus, glimepiride should have a more stable binding with the main protease of SARS-CoV-2 than ritonavir, indinavir, and atazanavir; and comparable stable binding with respect to boceprevir. The compound showed two conventional H-bond with Met49 and Glu166 amino acids (Figure 1). The sulfonylurea group of the compound is stabilized by a π-sulfur bond with His48 amino acid. Finally, the compound got stability by the π-alkyl interactions with Cys145 and Met165 amino acids.

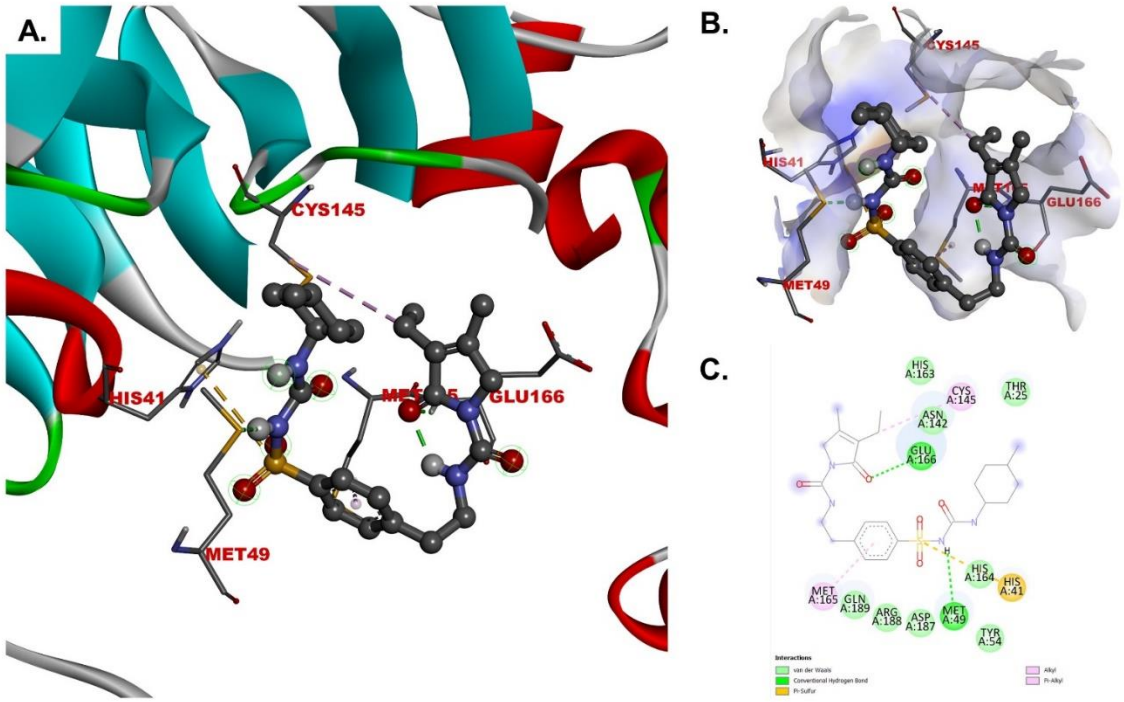

Figure 1: Docking interaction of Glimepiride with Main Protease protein of SARS-CoV-2 (PDB ID: 7BRP) A: The 3D interaction of the Glimepiride, presented in a ball and stick format, with the Main Protease protein of SARS-CoV-2. The interacting amino acids are labeled in red color and represented in the stick format. The Main Protease protein of SARS-CoV-2 is presented in a solid ribbon format with a characteristic color. B: Glimepiride presented in the binding pocket of the receptor. C: The 2D interaction of Glimepiride with the Main Protease protein of SARS-CoV-2.

3.2.2. Binding Interaction of Glimepiride with Papain-like Protease of SARS-CoV-2

Glimepiride showed good binding interaction with the papain-like protease with interaction energy of (-) 9.2 kcal/mol whereas, the four standard molecules ritonavir, indinavir, boceprevir and atazanavir showed the interaction energy of (-) 7.2 kcal/mol, (-) 8.0 kcal/mol, (-) 7.1 kcal/mol and (-) 7.0 kcal/mol respectively. The compound showed three hydrogen bonds of which two hydrogen bonds are with Gly266 amino acid and the other one with Tyr268 amino acid (Figure 2). The stability of the compound was accomplished by a π-π T-shaped interaction with Tyr268 amino acid, followed by π-alkyl interaction with Pro248 and Pro299 amino acids.

3.2.3. Binding Interaction of Glimepiride with RNA Dependent RNA Polymerase of SARS-CoV-2

Glimepiride showed very good binding interaction with the RNA Dependent RNA Polymerase with interaction energy of (-) 8.2 kcal/mol whereas, the four standard molecules ritonavir, indinavir, boceprevir and atazanavir showed the interaction energy of (-) 7.1 kcal/mol, (-) 7.5 kcal/mol, (-) 6.8 kcal/mol and (-) 6.2 kcal/mol respectively. The compound went deep inside the binding pocket of the RNA dependent RNA polymerase (Figure 3). A potent π-cation interaction has been observed with Lys500 amino acid. The compound is stabilized by four conventional H-bonds with Asn496, Lys500, Lys577 and Arg569 amino acids respectively.

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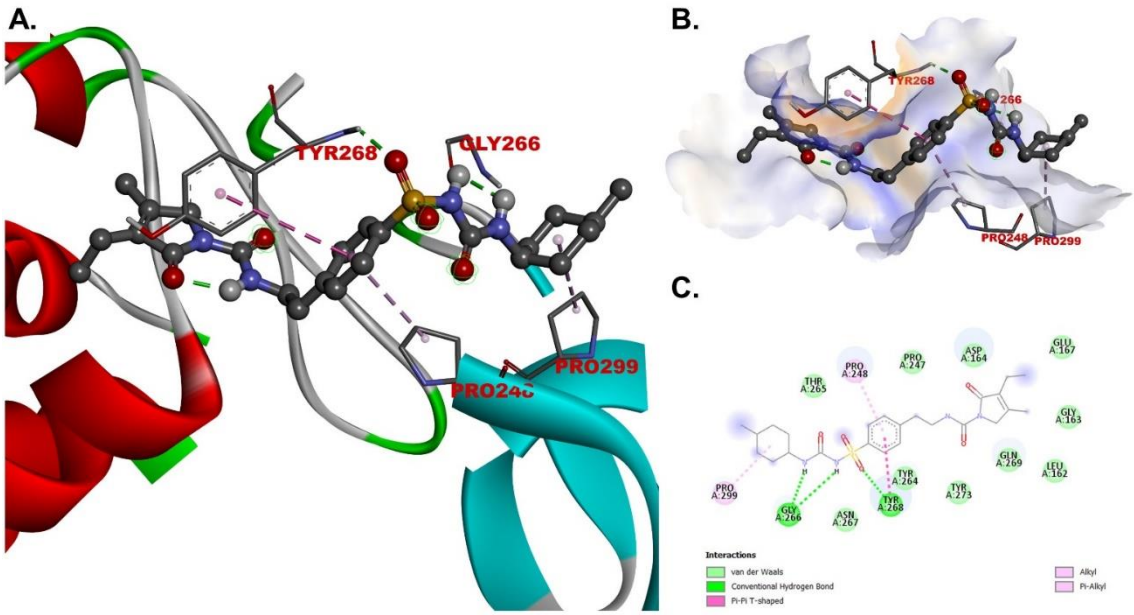

Figure 2: Docking interaction of Glimepiride with Papain-like Protease protein of SARS-CoV-2 (PDB ID: 7CMD) A: The 3D interaction of the Glimepiride, presented in a ball and stick format, with the Papain-like Protease protein of SARS-CoV-2. The interacting amino acids are labeled in red color and represented in the stick format. The Papain-like Protease protein of SARS-CoV-2 is presented in a solid ribbon format with a characteristic color. B: Glimepiride presented in the binding pocket of the receptor. C: The 2D interaction of Glimepiride with the Papain-like Protease protein of SARS-CoV-2.

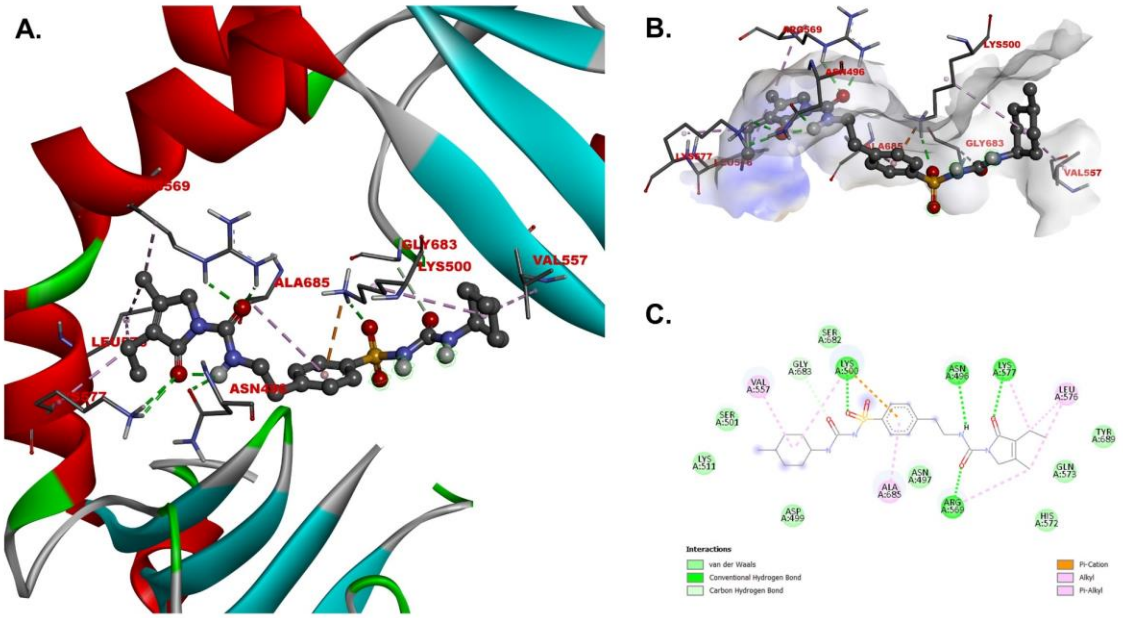

Figure 3: Docking interaction of Glimepiride with RNA Dependent RNA Polymerase protein of SARS-CoV-2 (PDB ID: 7D4F) A: The 3D interaction of the Glimepiride, presented in a ball and stick format, with the RNA Dependent RNA Polymerase protein of SARS-CoV-2. The interacting amino acids are labeled in red color and represented in the stick format. The RNA Dependent RNA Polymerase protein of SARS-CoV-2 is presented in a solid ribbon format with a characteristic color. B: Glimepiride presented in the binding pocket of the receptor. C: The 2D interaction of Glimepiride with the RNA Dependent RNA Polymerase protein of SARS-CoV-2.

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3.3. Molecular Properties and Drug-Likeness

The drug-likeness and molecular properties of the top compounds were measured in terms of physicochemical properties, Lipinski's Rule of Five, and Veber's Rule (Table 3) [50, 51]. Three out of four top docked compounds (glimepiride, glipizide and glisenide) have molecular weight less than 500 g/mol i.e. 490.60 g/mol, 445.54 g/mol, and 445.53 g/mol whereas the compound gliquidone (527.63 g/mol) along with all four standard compounds have molecular weight higher than 500 g/mol. Glimepiride and glisentide along with all four stand drugs have more than 10 rotatable bonds. Glipizide and gliquidone have 10 and 9 rotatable bonds respectively. All the top docked compound as well as standard compounds showed H-bond acceptor and H-bond donor in the acceptable range. The Total polar surface are of all the compounds as well as the standards are more than 120 Å^2. All the compounds including the standard compounds showed very good Consensus Log $P_{o/w}$ (Average of all LogP) within the range of 1-5 except ritonavir (5.04). All the compounds showed no Blood Brain Barrier permiation and low GI absorption (except glisentide and indinavir showed high GI absorption). Except ritonavir all the compound follows the Lipinski's Rule of Five. Having TPSA more than 120 Å^2 and rotatable bond more than 10, no compound except glipizide and gliquidone follows the Veber's Rule.

Table 3: Molecular Properties and Drug Likeness of the Top Compounds:

Compound Name	MW (g/mol)	Rotatable Bond	H-Bond Acceptor	H-Bond Donor	TPSA (Å^2)	Consensus Log $P_{o/w}$	GI Abs	BBB Permeant	Lipinski's Rule	Veber's Rule
Glimepiride	490.62	11	5	3	133.06	2.76	Low	No	Yes	No (TPSA> 120 Å^2)
Glipizide	445.54	10	6	3	138.53	1.97	Low	No	Yes	Yes
Gliquidone	527.63	9	6	2	130.26	3.62	Low	No	Yes	Yes
Glisentide	445.53	11	5	3	121.98	2.72	High	No	Yes	No (TPSA> 120 Å^2)
Ritonavir	720.94	22	7	4	202.26	5.04	Low	No	No	No
Indinavir	613.79	14	7	4	118.03	2.76	High	No	Yes	No
Boceprevir	519.68	14	4	5	150.70	2.09	Low	No	Yes	No
Atazanavir	704.86	22	9	5	171.22	3.82	Low	No	No	No

Further detailed pharmacokinetic parameters of all the top compounds along with standards are represented in the table 4 [60]. All the compounds except glisentide and indinavir showed low GI absorption and impermeable to the Blood Brain Barrier (BBB). All the compound have very low Log K_P value (below -6.0), which suggest that all the compounds have very low permeability (almost impermeable) to the skin. Cytochrome P450 1A2 (CYP1A2) is a mixed function oxidase enzyme which involves mainly in the metabolism of xenobiotics in human body along with metabolism and synthesis of drugs like cholesterol, steroids and lipids [61]. All the top docked compounds do not inhibit the CYP1A2 and thus don't affect the xenobiotic, cholesterol, steroid and lipid metabolism. The Cytochrome P450 2C19 (CYP2C19) is also a mixed function oxidase enzyme, involved in the metabolism of xenobiotics, proton pump inhibitors (PPI) and anti-epileptic drugs [62]. All the top docked compounds along with standard compounds do not inhibit the CYP2C19 enzyme (except glisentide). Cytochrome P450 2C9 (CYP2C9) is the oxidase enzyme which involves in the metabolism of xenobiotics as well as endogenous compounds like fatty acids [63]. All the standard compounds do not inhibit the CYP2C9 enzyme whereas, the anti-diabetic drugs do inhibit, which suggests that the anti-diabetic drugs inhibit the metabolism of fatty acids and impede to convert it to glucose. Cytochrome P450 2D6 (CYP2D6) is the enzyme of the body which involves in the metabolism and elimination of most of the drugs mainly through hydroxylation, demethylation, and dealkylation processes [64]. All the standard drugs along with glimepiride do not inhibit the CYP2D6 enzyme whereas the other three top docked drugs do inhibit the CYP2D6 which means they may stop elimination of other drugs. Cytochrome P450 3A4 (CYP3A4) is the oxidase enzyme of the body which involves in the metabolism and elimination of toxins from the body [65]. All the top compounds including the standard molecules inhibit the CYP3A4 enzyme (except indinavir). From the detailed pharmacokinetic analysis it can be said that the compound glimepiride is the better compound among all the considered anti-diabetic drugs.

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Table 4: Pharmacokinetic Parameters of all the Top Docked Compounds:

Compound Name	GI Absorption	BBB Permeant	P-gp Substrate	CYP1A2 Inhibitor	CYP2C19 Inhibitor	CYP2C9 Inhibitor	CYP2D6 Inhibitor	CYP3A4 Inhibitor	Log K_p
Glimepiride	Low	No	Yes	No	No	Yes	No	Yes	-6.56
Glipizide	Low	No	Yes	No	No	Yes	Yes	Yes	-7.66
Gliquidone	Low	No	Yes	No	No	Yes	Yes	Yes	-6.23
Glisentide	High	No	Yes	No	Yes	Yes	Yes	Yes	-6.52
Ritonavir	Low	No	Yes	No	No	No	No	Yes	-6.40
Indinavir	High	No	Yes	No	No	No	No	No	-7.97
Boceprevir	Low	No	Yes	No	No	No	No	Yes	-7.23
Atazanavir	Low	No	Yes	No	No	No	No	Yes	-6.62

In the first glance of bioavailability radar it was observed that the phycochemical properties of all the top docked compounds are within the saturation range with mild deviation in the FLEX point (Figure 4). All the standard compounds falls out of the saturation range of the radar. Thus, it can be said that all the top docked drugs have far better physicochemical properties than the standard drugs.

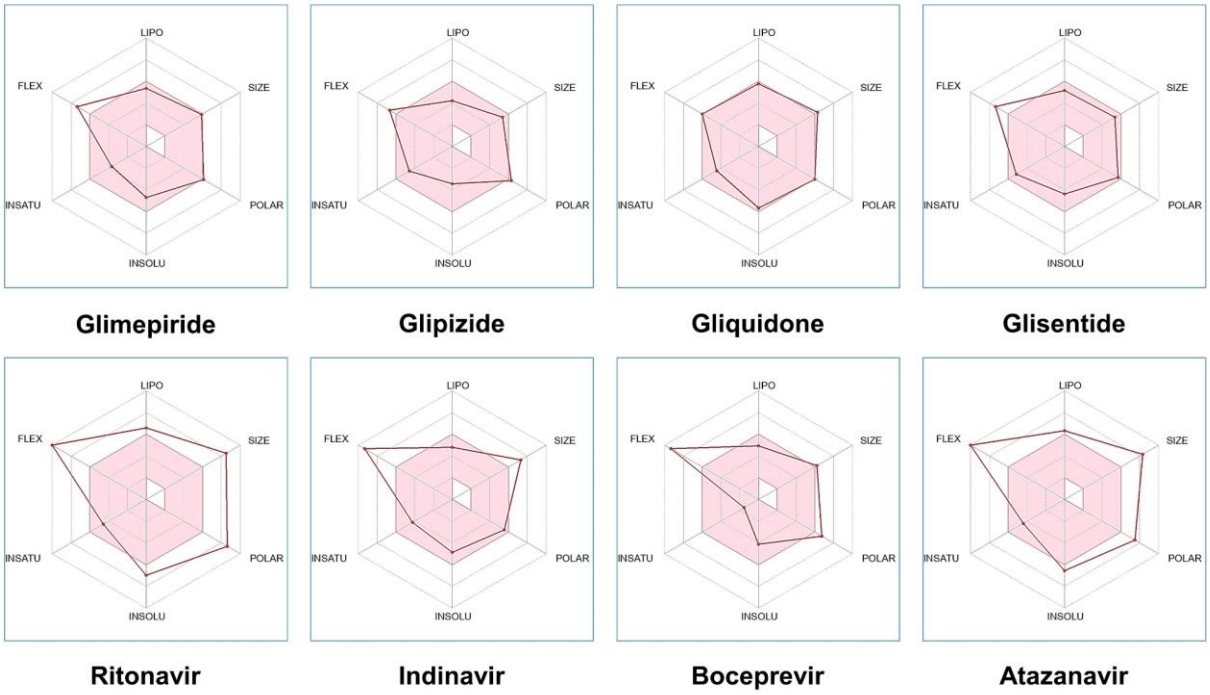

Figure 4: Drug Likeness of the Top Molecule at First Glance of Bioavailability Radar.

The BoiledEgg representation of the compounds reveals that glisentide along with the standard drug indinavir have the best pharmacokinetic parameter that falls between the GI and BBB (Figure 5), which means that the compounds can easily pass the GI tract and go to the blood circulation but, can't cross the BBB. The compound glimepiride, glipizide and gliquidone along with standard drug boceprevir showed absorption very near to the GI membrane (poorly permeable). The standard compound atazanavir is impermeable to GI tract as well as BBB. Finally, the standard compound showed pharmacokinetic parameter out of the BoiledEgg range. Thus, it can be said that all the top docked compounds have good pharmacokinetic parameter in terms of BoiledEgg representation.

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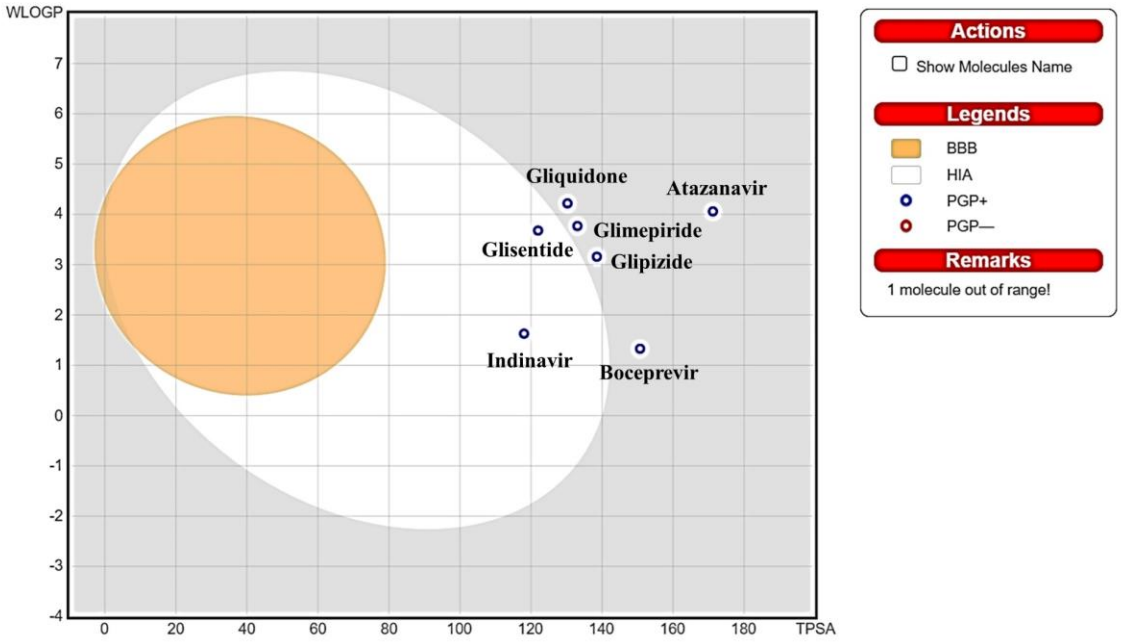

Figure 5: BoiledEgg presentation of the top 4 compounds along with standards.

3.4. Toxicity Studies

The toxicity study of all the top docked compounds was checked in the mcule toxicity checker web server (https://mcule.com/apps/toxicity-checker/) and the report revealed that all the compounds are non-toxic in nature. The detailed toxicity studies were carried out on the ProTox-II web server (https://tox-new.charite.de/protox_II/) [54]. The result parameters of the toxicity studies are reported in table 5. The toxicity of glimepiride falls under the toxicity class 5 whereas, the other three drugs glipizide, gliquidone and glisentide showed the toxicity level of class 6. Among all the standard drugs indinavir showed the toxicity level under class 5, ritonavir and boceprevir showed the toxicity under class 4 and atazanavir showed the toxicity class 3. Glimepiride showed inactive toxicity report for all the classes of toxicity with the LD_{50} value of 4000 mg/kg body weight. The probability of hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity of the compound was found to be 0.71, 0.72, 0.99, 0.76 and 0.64 respectively. Glipizide showed inactive toxicity report for all the classes of toxicity with the LD_{50} value of 15000 mg/kg body weight. The probability of hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity of the compound was found to be 0.63, 0.76, 0.96, 0.89 and 0.65 respectively. Gliquidone showed inactive toxicity report for all the classes of toxicity with the LD_{50} value of 15000 mg/kg body weight. The probability of hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity of the compound was found to be 0.59, 0.69, 0.51, 0.68 and 0.63 respectively. Glisentide showed inactive toxicity report for all the classes of toxicity with the LD_{50} value of 15000 mg/kg body weight. The probability of hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity and cytotoxicity of the compound was found to be 0.62, 0.73, 0.92, 0.78 and 0.77 respectively. All the top docked compounds showed notable less toxicity than all the four standard drugs. Further, the toxicity radar of all the top docked drugs along with standards are represented in figure 6 where at one glance all the toxicity parameters can be observed.

Table 5: Toxicity Probability of all the top docked compounds.

Compound Name	Hepatotoxicity Probability	Carcinogenicity Probability	Immunotoxicity Probability	Mutagenicity Probability	Cytotoxicity Probability	Predicted LD_{50} (mg/kg)
Glimepiride	0.71	0.72	0.99	0.76	0.64	4000
Glipizide	0.63	0.76	0.96	0.89	0.65	15000
Gliquidone	0.59	0.69	0.51	0.68	0.63	15000

Glisentide	0.62	0.73	0.92	0.78	0.77	15000
Ritonavir	0.73	0.62	0.97	0.70	0.63	1000
Indinavir	0.72	0.63	0.97	0.75	0.69	5000
Boceprevir	0.76	0.60	0.94	0.64	0.75	1500
Atazanavir	0.51	0.56	0.97	0.65	0.60	200

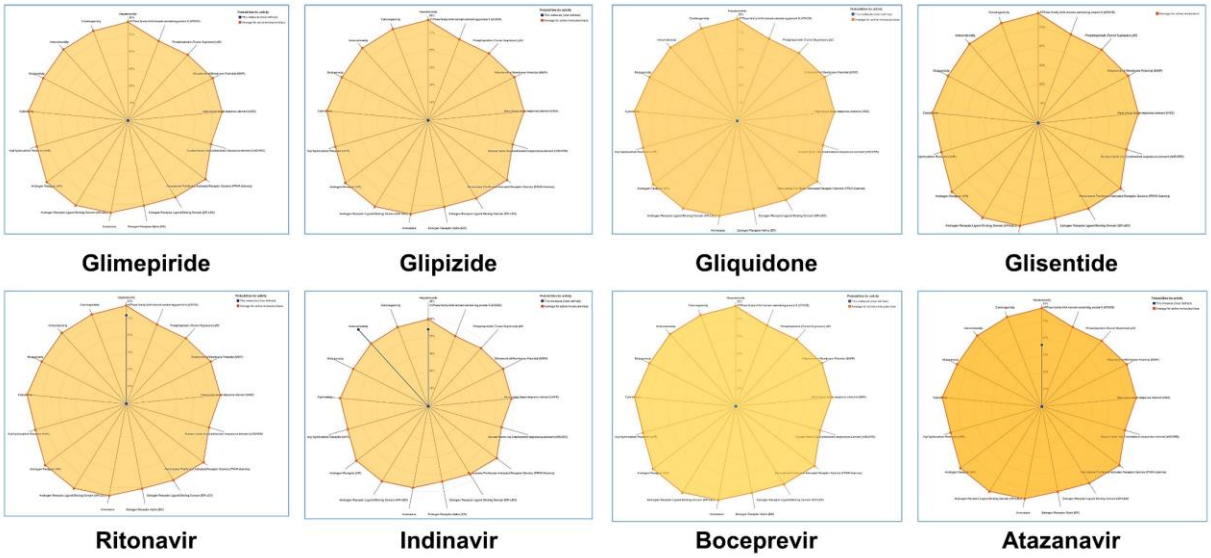

Figure 6: Toxicity Radar of top docked compounds along with standard compounds.

4. CONCLUSION

The antiviral agents like ritonavir, indinavir, boceprevir, atazanavir are being used to treat the SARS-CoV-2, have many drawbacks and allowed to use in emergency purpose only. These compounds may affect the diabetic patients in many norms. The antidiabetic drugs also can inhibit the three main enzymes of SARS-CoV-2 potentially and may show potential effect. However, further studies are required for the recommendation of these drugs to the patients. The glimepiride have very good docking score against all the three receptors of SARS-CoV-2. Glisentide with good docking score showed best pharmacokinetic parameter among all the molecules. All the top four compounds are belongs to the class of sulfonyl urea and thus, we suggest that sulfonyl urea containing anti-diabetic compounds may be preferred in diabetic patients at the time of SARS-CoV-2 pandemic and the chances of comorbidity can be eschewed.

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Conflicts of interests

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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